Remarks

Claims 1-4, 6-9, 11, 12, 14, 15, 18-21, 23-31, and 43-57 were pending in the subject application. By this Amendment, claims 1, 4, and 43 have been amended, and new claims 58-65 have been added. The undersigned avers that no new matter is introduced by this amendment. Entry and consideration of the amendments presented herein is respectfully requested. It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of the applicants' agreement with or acquiescence in the Examiner's position. Accordingly, claims 1-4, 6-9, 11, 12, 14, 15, 18-21, 23-31, and 43-65 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

Submitted herewith is a Request for Continued Examination (RCE) under 37 C.F.R. §1.114 for the subject application. Also submitted herewith is a supplemental Information Disclosure Statement (IDS), accompanied by the form PTO/SB/08 and copies of the references listed therein. The applicants respectfully request that the references listed on the form PTO/SB/08 be considered and made of record in the subject application.

Claim 1 has been amended for grammar. Claim 4 has been amended to correct a typographical error. Line 2 of claim 43 has been amended to recite "a patient" to provide antecedent basis for recitation of "the patient" in line 6 of the claim. Support for new claims 58-65 can be found, for example, at page 12, lines 6-14, of the subject specification.

Claims 1, 4, 9, 11, 14, 15, 18, 20, 27, 28, 30, 31, 43-48, and 51-56 have been rejected under 35 U.S.C. §102(a) as being anticipated by Kumar *et al.* (*J. Allergy Clin. Immunol.*, 2001, 108:402-408). The applicants respectfully submit that the Kumar *et al.* publication does not anticipate the claimed invention.

The applicants respectfully traverse these grounds for rejection and submit that the Kumar *et al.* publication is not prior art to the claimed invention. As the Examiner is undoubtedly aware, the requirements for authorship and inventorship are not the same. The inventorship of the claimed invention and the authorship of the Kumar *et al.* publication differ in that although Drs. Aruna K. Behera, Jianan Hu, and Richard Lockey are co-authors of the Kumar *et al.* publication, they are not

inventors on the subject application. Thus, Drs. Shyam S. Mohapatra and Mukesh Kumar are co-authors of the Kumar *et al.* publication and are inventors on the subject application.

Submitted herewith is a Declaration under 37 C.F.R. § 1.132 by Dr. Mohapatra for the Examiner's consideration. Dr. Mohapatra explains in his Declaration that although Drs. Aruna K. Behera, Jianan Hu, and Richard Lockey were each acknowledged as co-authors of the Kumar *et al.* publication, they did not contribute to the conception of the claimed invention. Therefore, despite their helpful assistance in carrying out research and/or preparation of the Kumar *et al.* publication, they were not included as co-inventors on the subject application.

The subject matter pertaining to the claimed invention that is described within the Kumar *et al.* publication was invented by the named inventors, *i.e.*, Drs. Shyam S. Mohapatra and Mukesh Kumar. Therefore, the Kumar *et al.* publication represents the inventors' own disclosure of their invention published less than one year prior to the filing date of the subject application.

"[O]ne's own invention, whatever the form of disclosure to the public, may not be prior art against oneself, absent a statutory bar." *In re Facius,* 161 USPQ 294, 301 (CCPA 1969); and MPEP §715.01(c). Therefore, under the authority of *In re Facius*, the disclosure contained in the Kumar *et al.* publication cannot be used as a reference against the applicants' claimed invention.

Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §102(a) is respectfully requested.

Claims 1-10, 12-14, 20-29, 43-45, 47, 49, 50, and 54-57 have been rejected under 35 U.S.C. §103(a) as being obvious over Hogan *et al.* (*Eur. J. Immunol*, 1998, 28:413-423) and further in view of Li *et al.* (*J. Immunol.*, 1996, 157:3216-3219) and Dow *et al.* (U.S. Patent No. 6,693,086). The applicants respectfully submit that the claimed invention is not obvious over the cited references.

The specification teaches, and claim 1 recites, that administration of a nucleic acid sequence encoding IL-12 and a nucleic acid sequence encoding IFN-γ effectively increases Th1-type cytokine production and decreases Th2-type cytokine production. The cited references provide no reasonable expectation of achieving this result. Moreover, as indicated at page 30, lines 3-4, of the subject specification, and shown in Figure 3C, administration of plasmids encoding IL-12 and IFN-γ resulted in a synergistic shift in cytokine profile.

At page 8, the outstanding Office Action states

> ... applicant has not indicated why the skilled practitioner would not expect that IL-12 and IFN-γ would interact to produce a synergistic effect given that Hogan *et al.* teaches that IL-12 upregulates ILN-γ [sic] production, which is vital for protection from allergic airways disease. This suggests that the two cytokines have complex interactions/regulatory roles that are more likely to be synergistic than additive in effect.

The applicants respectfully submit that there is nothing in the cited references to suggest that administration of a nucleic acid sequence encoding IL-12 and a nucleic acid sequence encoding IFN-gamma would have a synergistic effect. Dr. Mohapatra explains in his Declaration that, "while it is true that IL-12 and IFN-gamma have complex interactions and regulatory roles, this does not mean that delivery of nucleic acids encoding these two cytokines is more likely to have a synergistic effect, and synergy certainly would not be expected by one of ordinary skill in the art." Figure 3C is a graph showing an analysis of the dominant cytokine pattern after cytokine DNA vaccination in a mouse model. To examine the dominant pattern of cytokine responses, IFN-gamma/IL-4 and IL-2/IL-4 ratios were compared among different groups of mice. The results indicate that the net cytokine balance shifted in favor of the Th1-type response in cytokine-vaccinated mice; however, this shift was significantly greater in the group vaccinated with the combination of IFN-gamma and IL-12. Moreover, Figure 3C shows that the ratio of IFN-gamma/IL-4 was increased beyond what would be expected from the additive effects of IL-12 and IFN-gamma, individually. As indicated by Dr. Mohapatra, the benefits of the claimed method and compositions are unexpected in view of the cited references, and have a significant, practical advantage for immunotherapy.

Hogan *et al.* showed that the effectiveness of IL-12 was dependent upon the presence of IFN-gamma gene expression. The Hogan *et al.* publication describes a single experiment showing that vaccinia virus-mediated delivery and expression of the IL-12 gene significantly decreased the number of BAL eosinophils only if mice had the IFN-gamma gene. Referring to Hogan *et al.*, Dr. Mohapatra states in his Declaration,

> From this experiment, one of ordinary skill in the art would conclude that to exert its effect on eosinophilia, IL-12 requires the IFN-gamma gene to be present and that IL-12 presumably acts by inducing IFN-gamma gene expression. One of ordinary skill in the art would not interpret these results to demonstrate or suggest that exogenous

> delivery of IL-12 and IFN-gamma genes together provide a synergistic effect. (paragraph 6, page 4, Mohapatra Declaration)

Prior to the inventors' work described in the Kumar *et al.* publication, the following was known in the field: (1) IL-12 gene transfer by itself was able to decrease eosinophilia, presumably by shifting the immune response from a Th2-type to a Th1-type, but this required a functional IFN-gamma gene; and (2) the IFN-gamma gene also, by itself, decreased eosinophilia and airway hyper-reactivity, and shifted the Th2-type response to the Th1-type response. By individually administering 100 micrograms of cytokine-encoding plasmids per mouse, the subject application verifies that these two observations are correct. Furthermore, as explained by Dr. Mohapatra in his Declaration, when the inventors administered both plasmids together at half of the dosage (50 micrograms of each cytokine-encoding plasmid per mouse), a synergistic effect was observed (shown in Figure 3C). As explained by Dr. Mohapatra,

> From the previous data, we would have reasonably expected a result similar to that of either IL-12 or IFN-gamma administered individually. Thus, at the time the application was filed, based on all previous reports, one of ordinary skill in the art would expect that administering the combination of IL-12 and IFN-gamma-encoding plasmids at half amounts (50 micrograms each per mouse) would yield effects similar to that of IL-12 or IFN-gamma alone. Also, neither an additive nor a synergistic effect would be expected or reasonably predicted from the combination of IL-12 and IFN-gamma-encoding plasmids at 100 micrograms per mouse, because doubling the dose could easily lead to toxicity. (paragraph 6, pages 4-5, Mohapatra Declaration)

It is well settled in patent law that "a greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness ... of the claims at issue" *In re Corkill*, 226 USPQ 1005 (Fed. Cir. 1985). Evidence of a greater than expected result may be shown by demonstrating an effect which is greater than the sum of each of the effects taken separately (*i.e.*, demonstrating "synergism"). *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied*, 493 U.S. 975 (1989).

The benefits of the claimed method and compositions are unexpected in view of the cited references, and have a significant, practical advantage for immunotherapy. Therefore, the applicants respectfully submit that the claimed invention is not obvious over the prior art.

In view of the foregoing remarks, reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a) is respectfully requested.

Claims 2, 3, 6, 8, 12, 21, 23, 24, 26, 29, 50, and 57 have been rejected under 35 U.S.C. §103(a) as being obvious over Kumar *et al.* in view of Hogan *et al.*, Carroll *et al.* (*J. Nat. Cancer. Inst.*, 1998, 90:1881-1887), Genbank Accession No. B38957, Genbank Accession No. X13274, Maroun (U.S. Published Patent Application No. 2003/0138404), and Thill *et al.* (European Patent Application No. EP 0 343 388). The applicants respectfully submit that the claimed invention is not obvious over the cited references.

The prior art rejection under §103(a) relies on the Kumar *et al.* publication as the primary reference. As indicated above in the applicants' remarks concerning the rejection under 35 U.S.C. §102(a), the Kumar *et al.* publication represents the inventors' own disclosure of their invention published less than one year prior to the filing date of the subject application. Therefore, the applicants respectfully submit that the Kumar *et al.* publication is not prior art to the claimed invention and, under the authority of *In re Facius*, the disclosure contained in the Kumar *et al.* publication cannot be used as a reference against the applicants' claimed invention.

The applicants' remarks above concerning the rejection under U.S.C. §103(a) are incorporated herein by reference in their entirety. As explained by Dr. Mohapatra in his Declaration, the combined administration of plasmids encoding IL-12 and IFN-γ resulted in a synergistic shift in cytokine profile (as shown in Figure 3C) and, thus immune response, which would not have been expected by one of ordinary skill in the art at the time the subject application was filed. The benefits of the claimed method and compositions are unexpected in view of the cited references, and have a significant, practical advantage for immunotherapy. Therefore, the applicants respectfully submit that the claimed invention is not obvious over the prior art.

In view of the foregoing remarks, reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a) is respectfully requested.

In view of the foregoing remarks and amendments to the claims, the applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

The applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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GPL/mv
Attachments: Petition and Fee for Extension of Time
Request for Continued Examination
Amendment Transmittal Letter
Declaration by Dr. Mohapatra under 37 C.F.R. §1.132, with Exhibit A
Supplemental Information Disclosure Statement, form PTO/SB/08, and references